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(57) Abstract

Use of 5–HT$_6$ receptor antagonists for the preparation of medicaments for the treatment of Parkinson disease.

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Use

The present invention relates to the use of 5-HT_6 receptor antagonist compounds in the treatment of certain CNS disorders. More particularly the invention relates to the use of such compounds in the treatment of Parkinson's disease.

Parkinson's Syndrome refers to a collection of neurodegenerative diseases that are characterised by a disturbance of voluntary movement, and which includes both Idiopathic Parkinson's disease and Multiple System Atrophy. Typical features of these diseases are that muscles become stiff and sluggish, movement becomes clumsy and difficult and uncontrollable rhythmic twitching of groups of muscles produces characteristic shaking or tremor. Parkinson's disease is also associated with cognitive dysfunction and, in a proportion of cases, concurrent dementia. These conditions are believed to be caused by extensive degeneration of the dopaminergic nigrostriatal tract. The absence of adequate release of the chemical transmitter dopamine during neuronal activity thereby leads to the Parkinsonian symptomatology.

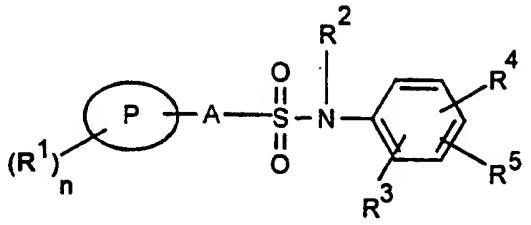
WO 98/27081, WO 98/27058 and WO 99/02502 all disclose compounds that are said to possess 5-HT_6 receptor antagonist activity. These compounds are alleged to be of use in the treatment of various CNS disorders. EPA 0815861 and EP 0930302 disclose sulphonamide and sulphone compounds respectively that are to said to possess 5-HT_6 receptor antagonist activity and are claimed to be useful in the treatment of various CNS disorders including Parkinson's disease. EP 0299602B1 discloses certain indolone derivatives that are useful in the treatment of Parkinson's disease and, advantageously, have anti-depressant and anxiolytic effects.

It has now been found that certain compounds, known in the art as 5-HT_6 receptor antagonists, selectively increases activity of the nigrostriatal pathway and consequently have utility in the treatment of Parkinson's disease. In addition, the compounds of the present invention have additional effects on the central nervous system, namely, cognitive effects. In particular, the cognitive effects of the compounds of the present invention are perceived to be advantageous as patients receiving current therapies often also need to take separate medication for the treatment of cognitive dysfunction and dementia. The presence of such qualities as a single compound may therefore reduce the need for such separate therapies.

The present invention therefore provides, in a first aspect, the use of a compound having 5-HT_6 receptor antagonist activity in the manufacture of a medicament for use in the treatment of Parkinson's Disease characterized in that the compound having 5-HT_6

receptor antagonist activity is selected from the group consisting of a compound of formula (A), (B) or (C)

Compound of Formula (A)



(A)

wherein:

P is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C_{1-6}alkylene or a C_{1-6}alkenylene group;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more halogen atoms, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, nitro, amino, C_{1-6}alkylamino or diC_{1-6}alkylamino, cyano or R^1 is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

n is 0, 1, 2, 3, 4, 5 or 6,

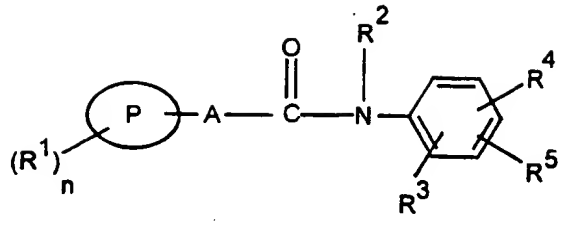
R^2 is hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl;

R^3 is a group R^5 or together with R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ or R^3 is linked to R^2 to form a group $(CH_2)_2$ or $(CH_2)_3$;

R^4 is $-X(CH_2)p-R^6$ where X is a single bond, CH_2, O, NH or N- C_{1-6} alkyl and p is 0 to 6 and R^6 is an optionally substituted 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl; and

R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, nitro, trifluoromethyl, cyano or aryl.

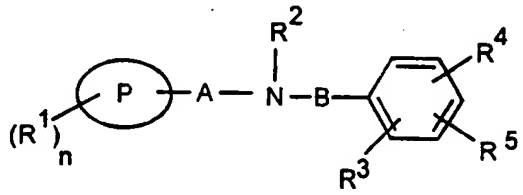
Compounds of Formula (B)



(B)

where $R^1 - R^5$, P, A and n are as defined in formula (A)

Compounds of Formula (C)



(C)

wherein:

P is phenyl, naphthyl, anthracenyl, a bicyclic heterocyclic ring, a tricyclic heteroaromatic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C_{1-6}alkylene or a C_{1-6}alkenylene group;

B is SO_2;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more fluorine atoms, C_{3-6}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, nitro, cyano, $NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_{1-6}alkyl or optionally substituted phenyl, SR^{11} where R^{11} is as defined above or R^1 is optionally substituted phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur, or R^1 together with a second R^1 substituent forms a group -O-CH_2-O-, OCH_2CH_2O-, -$CH_2CH_2CH_2$– or -$CH_2CH_2CH_2CH_2$-,

n is 0, 1, 2, 3, 4, 5 or 6;

R^2 is hydrogen, C_{1-6}alkyl, arylC_{1-6} alkyl or together with group P form a 5 to 8 membered ring optionally substituted with one or more C_{1-6}alkyl groups;

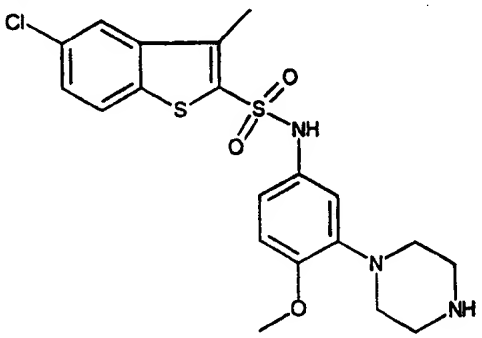
R^3 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy optionally substituted with one or more fluorine atoms, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, , nitro, trifluoromethyl, cyano or aryl or together with the group R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ optionally substituted with 1 or more C_{1-6}alkyl groups;

R^4 is $-X(CH_2)p-R^6$ where X is a single bond, CH_2, O, NH or N-alkyl and p is 0 to 6 and R^6 is an optionally substituted 4- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6} alkyl or arylC_{1-6}alkyl; and

R^5 is a group R^3 or together with R^3 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ optionally substituted with 1 or more C_{1-6}alkyl groups.

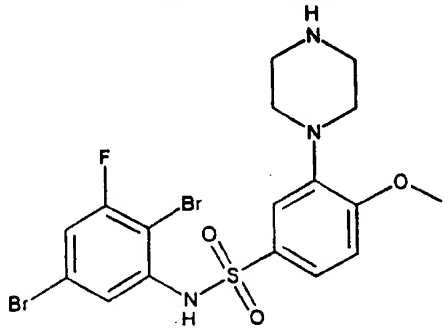
The preferred compounds for use in this invention demonstrate greater than 100-fold selectivity for 5-HT_6 receptors over other binding sites within the CNS, in particular, other 5-HT receptor sub-types and dopaminergic receptors. The selectivity of the compounds of this invention for 5-HT_6 receptors can be determined using binding assays methods which are well known to those skilled in the art.

Particularly preferred compounds of this invention include 5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide (Example 83 in WO 98/27081), that is to say, the compound of formula (I)



(I)

and *N*-(2,5-Dibromo-3-fluorophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulfonamide (Example 140 in WO 99/02502) that is to say, the compound of formula (II)



(II)

It will be apparent to those skilled in the art that compounds of formulas (A), (B) and (C) may form acid addition salts. Suitable examples include pharmaceutically

acceptable salts such as maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, sulphate, citric, lactic, mandelic, tartaric and methanesulphonic. Suitably, a compound of formula (I) or formula (II) is used as the hydrochloride salt.

Certain compounds of formulas (A), (B) and (C) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of these compounds and the mixtures thereof including racemates. Tautomers also form an aspect of the invention.

The compounds of formulas (A), (B) and (C) and their pharamaceutically acceptable salts can be prepared by the methods described in WO 98/27081, WO 98/27058 and WO 99/02502 respectively.

The compounds for use in this invention can be evaluated for anti – Parkinson activity using procedures known to those skilled in the art such as the MPTP treated marmoset model.

The compounds for use in this invention are expected to have utility in treating any condition characterized by degeneration of the dopaminergic nigrostriatal tract. Consequently, these compounds will be useful in the treatment of both Idiopathic Parkinson's disease and Multiple System Atrophy. Multiple System Atrophy includes olivopontocerebellar atrophy, striato-nigral degeneration type and Shy-Drager type atrophy.

The present invention further provides a method of treatment of Parkinson's Disease and other related disorders which comprises administering to a host in need thereof an effective amount of a compound of formula (A), (B) or (C) or a pharmaceutically acceptable salt thereof.

It will be appreciated by those skilled in the art that the compounds according to this invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, by co-administration with other anti-Parkinson's agents. Examples of such include levodopa or a dopamine agonists, and in particular, those described in EP 0299602B1.

When used in therapy, the compounds of formula (A), (B) or (C) are usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

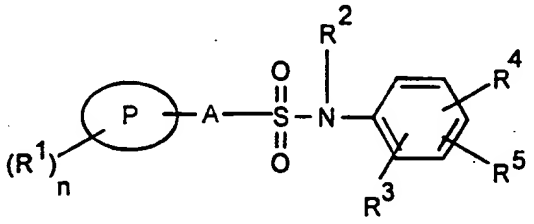
For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Suitably the compounds for use in this invention will be administered for a period of continuous therapy.

Claims:

1. The use of a compound having 5-HT_6 receptor antagonist activity in the manufacture of a medicament for use in the treatment of Parkinson's Disease characterized in that the compound having 5-HT_6 receptor antagonist activity is selected from the group consisting of a compound of formula (A), (B) or (C)

Compound of Formula (A)



(A)

wherein:

P is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C_{1-6}alkylene or a C_{1-6}alkenylene group;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more halogen atoms, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, nitro, amino, C_{1-6}alkylamino or diC_{1-6}alkylamino, cyano or R^1 is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

n is 0, 1, 2, 3, 4, 5 or 6,

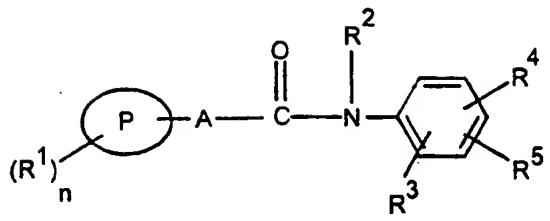
R^2 is hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl;

R^3 is a group R^5 or together with R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ or R^3 is linked to R^2 to form a group $(CH_2)_2$ or $(CH_2)_3$;

R^4 is $-X(CH_2)p-R^6$ where X is a single bond, CH_2, O, NH or N- C_{1-6} alkyl and p is 0 to 6 and R^6 is an optionally substituted 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl; and

R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, nitro, trifluoromethyl, cyano or aryl.

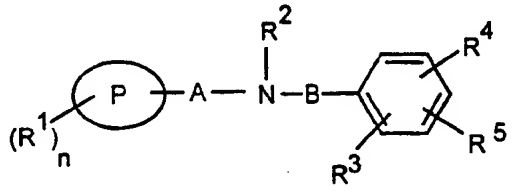
Compounds of Formula (B)



(B)

where $R^1 - R^5$, P, A and n are as defined in formula (A)

Compounds of Formula (C)



(C)

wherein:

P is phenyl, naphthyl, anthracenyl, a bicyclic heterocyclic ring. a tricyclic heteroaromatic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C_{1-6}alkylene or a C_{1-6}alkenylene group;

B is SO_2;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more fluorine atoms, C_{3-6}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, nitro, cyano, $NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_{1-6}alkyl or optionally substituted phenyl, SR^{11} where R^{11} is as defined above or R^1 is optionally substituted phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur, or R^1 together with a second R^1 substituent forms a group -O-CH_2-O-, OCH_2CH_2O-, -$CH_2CH_2CH_2$– or -$CH_2CH_2CH_2CH_2$-,

n is 0, 1, 2, 3, 4, 5 or 6;

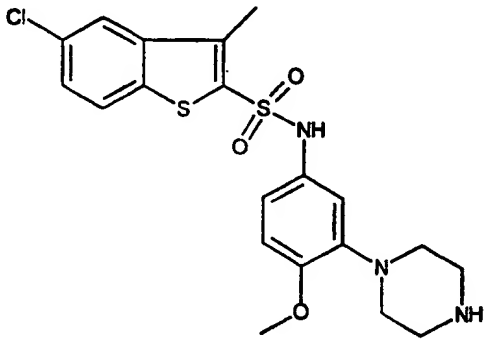
R^2 is hydrogen, C_{1-6}alkyl, arylC_{1-6} alkyl or together with group P form a 5 to 8 membered ring optionally substituted with one or more C_{1-6}alkyl groups;

R^3 is hydrogen. halogen. C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkanoyl. C_{1-6}alkoxy optionally substituted with one or more fluorine atoms. hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy. . nitro. trifluoromethyl. cyano or aryl or together with the group R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ optionally substituted with 1 or more C_{1-6}alkyl groups;

R^4 is $-X(CH_2)p-R^6$ where X is a single bond, CH_2, O, NH or N-alkyl and p is 0 to 6 and R^6 is an optionally substituted 4- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6}alkyl or arylC_{1-6} alkyl; and

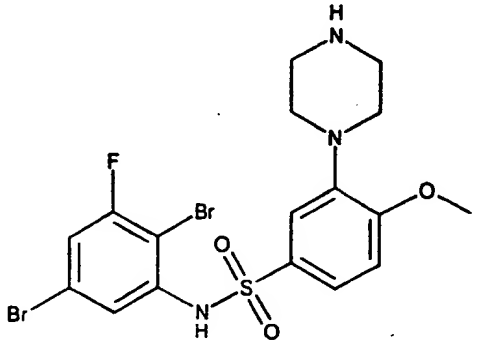
R^5 is a group R^3 or together with R^3 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ optionally substituted with 1 or more C_{1-6}alkyl groups.

2. The use according to claim 1 wherein the 5-HT_6 receptor antagonist is the compound of formula (I) - 5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide or a pharmaceutically acceptable salt thereof



(I)

3. The use according to claim 1 wherein the 5-HT_6 receptor antagonist is the compound of formula (II) - *N*-(2,5-Dibromo-3-fluorophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulfonamide or a pharmaceutically acceptable salt thereof



(II)

4. A pharmaceutical composition for use in the treatment of Parkinson's Disease which comprises a compound described in any one of claims 1 - 3 and a pharmaceutically acceptable carrier.